RUNNING HEAD: Renewal of Avoidance

Renewal of fear and avoidance in humans to escalating threat: implications for translational research on anxiety disorders.

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Abstract

Exposure-based treatment for threat avoidance in anxiety disorders often results in fear renewal. However, little is known about renewal of avoidance. This multimodal laboratory-based treatment study used an ABA renewal design and an approach-avoidance (AP-AV) task to examine renewal of fear/threat and avoidance in twenty adults. In Context A, nine visual cues paired with increases in probabilistic money loss (escalating threats) produced increases in ratings of feeling threatened and loss expectancies and skin-conductance responses (SCR). During the AP-AV task, a monetary reinforcer was available concurrently with threats. Approach produced the reinforcer or probabilistic loss, while avoidance prevented loss and forfeited reinforcement. Escalating threat produced increasing avoidance and ratings. In Context B with Pavlovian extinction, threats signaled no money loss and SCR declined. During the AP-AV task, avoidance and ratings also declined. In a return to Context A with Pavlovian threat extinction in effect during the AP-AV task, renewal was observed. Escalating threat was associated with increasing ratings and avoidance in most participants. SCR did not show renewal. These are the first translational findings to highlight renewal of avoidance in humans. Further research should identify individual difference variables and altered neural mechanisms that may confer increased risk of avoidance renewal.

Key words: renewal, relapse, avoidance, fear, anxiety, approach-avoidance.

Anxiety disorders are among the most common type of mental disorder worldwide (Craske & Stein, 2016; GBD, 2016). Approximately one-tenth of adults, particularly women and those from Western cultures, meet criteria for an anxiety disorder each year (Baxter, Scott, Vos, & Whiteford, 2013). Treatment for anxiety disorders often involves exposure-based behavior therapy, whereby clients are presented with their fear relevant stimulus or situation in the absence of those directly experienced outcomes. The purpose of this exposure is that clients learn that the cues are in fact safe, which may then lead to a reduction in self-reported fear and avoidance (Hermans, Craske, Mineka, & Lovibond, 2006). Unfortunately, behavior change and symptom reduction may be short-lived, and relapse is common (Vervliet, Craske, & Hermans, 2013).

Fear and anxiety comprise a constellation of cognitive, behavioral and physiological responses that, at extreme levels of severity, can cross diagnostic thresholds (Craske & Stein, 2016). Avoidance is one particularly prominent behavioral pattern associated with anxiety disorders, and people with anxiety disorders often engage in avoidance of external threats and internal experiences, such as negative thoughts/feelings (American Psychiatric Association, 2013). Avoidance may limit completion of exposure therapy (Zayfert et al., 2005) and even interfere with the likely success of such treatment (Meulders, Van Daele, Volders, & Vlaeyen, 2016). Avoidance may also paradoxically increase self-reported fear, while excessive avoidance is likely to facilitate relapse of anxiety symptoms and coping strategies after therapy (Craske, Hermans, & Vervliet, 2018; Craske et al., 2008; Hermans et al., 2006). Indeed, while it is known that avoidance may promote return of fear and interfere with recovery from anxiety disorders (Craske et al., 2018; Treanor & Barry, 2017), evidence suggests that expanding the therapeutic focus from fear alone to include avoidance may lead to a better understanding of why exposure

treatments sometimes fail and lead to relapse (Carpenter, Pinaire, & Hofmann, 2019; Hofmann & Hay, 2018; Nakajima, 2014; Vervliet & Indeku, 2015). As Craske et al. (2018) highlighted, "albeit often underappreciated, return of fear is problematic only when accompanied by escape or avoidance behaviors. In the absence of escape or avoidance, return of fear would be followed by additional extinction and eventual fear reduction…the success of exposure treatment may be measured most accurately by the increase in approach [and decrease of avoidance] than by the decrease in fear." (p.7).

Translational research on fear and avoidance employs variants of Pavlovian threat conditioning and operant avoidance learning paradigms (Dymond, 2019; Dymond & Roche, 2009; LeDoux, Moscarello, Sears, & Campese, 2017; Lonsdorf et al., 2017; Vervliet et al., 2013). In Pavlovian threat conditioning, presentations of one arbitrary cue (a conditional stimulus or CS) are followed by an aversive event (unconditional stimulus or US) such as electrical shock, making it a cue for danger (CS+). Presentations of another cue are followed by the absence of the US, making it a cue for safety (CS-). The result is differentiated conditioned responding with increased responding elicited by CS+ over CS-, which declines to baseline levels when the US no longer follows the CS+ (a process called extinction or inhibitory learning; Craske et al., 2018).

However, extinction learning is itself not permanent. It is influenced by context, as seen in *renewal*, which occurs when a CS is encountered in a context other than where extinction learning occurred, such as either the original conditioning context (ABA renewal) or a novel context (ABC renewal; Bouton, 2002; Effting & Kindt, 2007). Importantly, renewal is not limited to aversive CSs. Renewal effects have been observed using appetitive stimuli (Rhodes & Kilcross, 2017; Kuroda, Mizutani, Cancado, & Podelsnik, 2017; Browning & Shahan, 2018) and

behavior maintained by positive reinforcement in laboratory and applied settings (Podelsnik, Kelley, Jimenez-Gomez, & Bouton, 2017; Wathen & Podelsnik, 2018).

Studying negatively reinforced avoidance within this arrangement involves providing opportunities to perform discrete responses (e.g., key pressing) in the presence of the CS+ to cancel or postpone upcoming US delivery (Dymond, 2019; LeDoux et al., 2017). Shock-avoidance responding is readily acquired under these circumstances, although it may appear excessive when it continues to occur despite the US being withheld or when non-avoidance is not followed by the US (termed *fear extinction*; Dymond, 2019). In this way, excessive avoidance precludes disconfirming opportunities with the feared situation or event and is likely therefore to contribute to the both the acquisition and persistence of anxiety.

Unfortunately, little is known about the renewal of avoidance and associations with fear renewal (Dymond, 2019; LeDoux et al., 2017; Urcelay & Prevel, 2019). This represents a significant gap in our knowledge base as preclinical and clinical research examining the conditions under which return of fear may facilitate a return of avoidance can broaden the current state of fear extinction and renewal research (Vervliet et al., 2013). Renewal of negatively reinforced escape behavior has been shown in laboratory research with adults (Alessandri, Lattal, & Cancado, 2015) and applied research with children diagnosed with autism (Kelley, Jimenez-Gomez, Podelsnik, & Morgan, 2018). But few studies have examined relations between fear renewal and avoidance renewal.

In one nonhuman study (Nakajima, 2014), rats in a shuttle box underwent Pavlovian fear conditioning in which an auditory cue became a conditioned threat (CS+) by predicting electric shock. In Context A, the threat cue was presented, and rats learned that crossing the midline of the shuttle box prevented shock delivery. In Context B, the threat cue was paired with no shock

and avoidance declined. During renewal testing in Context A, threat cue presentations with Pavlovian extinction in effect produced a significant increase in avoidance relative to Context B.

Related human studies have shown avoidance renewal following Pavlovian extinction with response prevention as well as instructions to not avoid (Vervliet & Indekeu, 2015). Renewal of avoidance can also be attenuated when a monetary cost is added to engage in avoidance (Vervliet, Lange, & Milad, 2017). Further, clinical studies with spider-fearful participants report a significant return of self-reported fear and behavioral avoidance (Rodriguez, Craske, Mineka & Hladek, 1999), but not elevated heart rate (Mineka, Mystkowski, Hladek, & Rodriguez, 1999; Mystkowski, Craske, & Echiverri, 2002), underscoring the complex relationship between fear and avoidance (Mineka, 1979). Moreover, there are reports of a return of self-reported shock expectancy, even when extinction had occurred in multiple contexts (Neumann, Lipp & Cory, 2007). In sum, there is ample evidence pointing to the renewal of avoidance following fear extinction in a different context.

With the broader aim of contributing to efforts to improve the efficacy of exposure-based treatment for anxiety disorders and reducing relapse, the purpose of this multimodal, laboratory-based treatment study was to examine fear/threat renewal and avoidance renewal. An ABA context renewal design was used along with an approach-avoidance (AP-AV) task, in which a monetary reinforcer was available concurrently with a series of escalating money loss threats that varied across trials (Schlund et al., 2016). During the AP-AV task, a monetary reinforcer was available concurrently with each threat. Approach choices produced a reinforcer or probabilistic loss, while avoidant choices prevented loss and forfeited possible reinforcement. The AP-AV paradigm affords the opportunity to study the effects of escalating threat on choices to transition from approach to avoidance and renewal of fear/threat and avoidance. In Context A, participants

underwent threat conditioning where they learned that escalating ‘threat levels’ on a vertical bar signaled greater probabilities of money loss. We predicted escalating threat would be associated with increases in skin-conductance response (SCR) and self-reported ratings of feeling threatened and loss expectancy. Next, participants completed an approach-avoidance (AP-AV) task. We predicted escalating threat would be associated with increases in the frequency of avoidance and decreases in the frequency of approach, along with increasing ratings. In Context B, we predicted Pavlovian extinction of threat, through pairing threat levels with no losses, would decrease SCR and ratings and reduce avoidance on the AP-AV task. During renewal testing in Context A with Pavlovian threat extinction in effect during the AP-AV task, we predicted renewal would occur such that escalating threat would be associated with increasing avoidance, SCR and ratings.

Method

Participants

Twenty adult participants (M_{age} = 22.1, *SD* = 1.9 years; 15 females) were recruited by community flyers and reported being free of psychiatric disorders, brain insult, neurological disorders and use of medications capable of altering central nervous system functioning. Participants were compensated $2.00 for participation and earned additional money on experimental tasks completed in the 2-hr session. This investigation was approved by the Institutional Review Board for the Protection of Human Subjects at the University of North Texas. All participants provided written informed consent.

Apparatus

The experiment took place in a small windowless room containing a desk, computer monitor, chair, and standard keyboard. Responses were made with the right hand on a number

pad. Experimental events were programmed, and data collected, with software written in the Eprime® platform. Skin conductance responses were acquired with a sampling rate of 100Hz using SHIMMER™ (Burns et al., 2010) from two disposable Ag/AgCl electrodes (2 cm diameter) attached to the base of thenar and hypothenar eminence of the left hand.

Procedure

The methods used closely modeled those used in a prior behavioral and functional neuroimaging investigation on avoidance (Schlund et al., 2016). At study outset, general instructions described the discrete trial AP-AV task for participants as making repeated decisions about whether to board (approach) or refuse to board spaceships (avoidance). To prompt choices, an onscreen alien 'threat meter' was available that highlighted the trial-by-trial probability an encountered spaceship was laden with aliens that would take participant's money and supplies. The task goal was to earn as much money as possible and prevent alien attacks. Total earnings depended upon choices and initial stipends, which varied to accommodate differences in gains and losses across conditions and generally prevent negative earnings. A within-subject ABA context renewal design was used with exposure to Contexts A and B equated in duration (e.g., Lovibond, Preston, & Mackintosh, 1984). Table 1 presents the order of conditions and dependent measures.

Figure 1 and Table 1 about here

Context A

Threat learning. A pretesting phase was designed to ensure levels on a vertical bar were viewed as neutral stimuli and responding was undifferentiated. In Figure 1, each of ten levels on

a vertical bar was highlighted with a “NOW” prompt and presented for six trials in a randomized order. Six additional trials prompted participants to “Press #3.” (These trials served as baseline trials for a related functional magnetic resonance imaging study and are irrelevant to the goals of the present study.) No labels were present on the vertical bar. Each trial consisted of a 3 s presentation followed by a 5-7 s jittered intertrial interval (ITI) and blank screen. Instructions were presented on a white background and emphasized paying attention to where a “<NOW>” prompt appeared on the vertical bar. Afterwards, pretest ratings of threat and loss expectancy were obtained for each threat level. The following instructions were printed on the computer screen and read aloud by the experimenter:

> “This is a 10-minute task. Your job is to pay attention. During the task, you will see several shapes on the screen. One shape is a standing rectangle. Every 9 s or so the word <NOW> will appear by the rectangle. You will also see PRESS #3 printed in the middle of the screen. When these occur, press number 3. That’s it. Very simple. It is important that you follow these directions. This task is very boring (sorry) so try to stay alert. What we are doing is measuring your skin-conductance when you see the word <NOW> and press #3. This information tells us about your unique level of reactivity. So, relax and please follow the instructions. If you don’t, it will ruin the data we do collect. Any questions? Experimenter press #6 to start the task.”

During threat learning, a modified Pavlovian fear conditioning paradigm lasting 10 min was utilized to produce differential conditioning. The table in Figure 1 shows levels 1-3 were paired with no loss (CS-). In contrast, levels 4-10 were paired with an increasing probability of loss (CS+). Task instructions were presented on a white background and stated that what participants would learn applied to a space region known as “Sector A.” Participants were given a large stipend of $25 and instructed to watch and learn where a “<NOW>” prompt appeared on the unlabeled vertical bar and whether a $1 loss prompt followed. Instructions emphasized that learning this relationship would be important for doing well later. Trials consisted of a 3 s level presentation, 750 ms outcome and a 5-7 s jittered ITI. Each threat level was presented for six

trials in a randomized order. During a posttest phase, ratings of threat and loss expectancy were obtained for each threat level. Threat learning was considered stable and ended when posttest ratings of loss expectancy showed an increasing trend across threat levels ratings. One participant required two 10-min training sessions. The following instructions were printed on the computer screen and read aloud by the experimenter:

"YOU ARE NOW IN SECTOR A. This is a 10-minute task. It is designed to prepare you for games you will play later. In this and the upcoming games, you fly through space Sector A and meet up with other ships. However, some ships contain aliens. You have a scanner that searches ships and displays the alien threat level. When a ship is found, the threat level will appear as <NOW>. In this task you must look at the threat level and learn how likely it is you will lose $1. All you need to do is watch. PAY ATTENTION!! DO NOT PRESS ANY BUTTONS. So, watch the threat level and note how often you DO and DO NOT lose $1. What you learn will help later on. For now, we will give you $25 but YOU WILL LOSE most of it now. Any questions? Experimenter press #6 to start the task."

Figure 2 about here

AP-AV practice. Figure 2 provides a schematic of the main AP-AV task. Task instructions appeared on a white background and stated that the spaceship was patrolling "Sector A." This 3 min training involved trial-and-error learning of the approach and avoidance contingencies. Each trial consisted of a 3 s choice period, 750 ms outcome and a 5-7 s jittered ITI. During the ITI, the screen contained a radar screen and the statement "Scanning for ships." On each trial, a $0.10 reinforcer was made available in the presence of one highlighted threat level displayed on the alien threat meter. Five trials with threat level 1 (p(loss) = 0.0) were presented followed by five trials of threat level 10 (p(loss) = 1.0). The goal was to train participants to use the highlighted threat level such that they pressed the approach button when at level 1 and pressed the avoidance button when at level 10. At level 1, approach produced a $0.10

reward, while avoidance maintained the threat level at 1. At level 10, approach produced a $1 loss, while avoidance lowered the threat level to 1. Training ended when approach occurred at level 1 on 4/5 trials and avoidance occurred at level 10 on 4/5 trials. All participants were required to meet the criterion within three runs before proceeding. The following instructions were printed on the computer screen and read aloud by the experimenter:

"YOU ARE NOW IN SECTOR A. This is a 3-minute PRACTICE game to prepare you for the real game. Your job is to earn money AND keep aliens from taking your money. If you quit early, you don't get any money from this task. In this game, you fly through space and meet up with other ships in Sector A. You have a scanner that searches ships and displays the alien threat level. SO: Remember what you learned earlier about the threat levels!! When a ship is found the threat level will appear as <NOW> Here is when you MUST make a CHOICE in less than 3 seconds: 1. You can board the ship by pressing #1 and you will earn $0.10 BUT the threat level will still exist! Or 2. You can avoid the ship and REDUCE the threat level to 1 by pressing #2. Finally, every once in a while, you will be told to <Press #3>. Please do so when asked. It is important. Any questions? Experimenter press #6 to start the task."

AP-AV task. All participants completed the 10 min AP-AV task once, followed by a short 3 min break**.** Task instructions appeared on a screen with a white background. AP-AV training instructions were used and edited to include the addition of a $5 stipend and increase in task length to 10 minutes. On each trial, a $0.10 reinforcer was made available in the presence of one highlighted threat level displayed on the alien threat meter. Six trials of each threat level were presented in a randomized order. Approach choices produced the $0.10 reinforcer or probabilistic loss, while avoidant choices lowered the threat level to 1, prevented loss and forfeited reinforcement. Instructions stated that failing to respond would produce the prompt "Lose $1", and $1 would be deducted from earnings. At completion, ratings of threat and loss expectancy were obtained for each threat level.

Context B

Threat Extinction. Threat Extinction was identical to the Threat Learning condition except that the task instructions appeared on screen with a yellow background. Instructions from the Threat Learning condition were used and edited to state participants were in "…SECTOR B" and the stipend was $3. In this case, the loss contingency for each conditioned threat level was suspended (i.e., Pavlovian threat extinction). Participants were not instructed about the extinction contingencies but were told to watch and learn what levels were highlighted and associated with loss. Afterwards, ratings of threat and loss expectancy were obtained for each threat level.

AP-AV task. Participants completed the 10 min AP-AV task with Pavlovian threat extinction in effect. Task instructions appeared on a screen with a yellow background. AP-AV training instructions were used and edited to state participants were in "…SECTOR B," the stipend was $5, and the task length was 10 minutes. On each trial, a $0.10 reinforcer was made available in the presence of one highlighted threat level displayed on the alien threat meter. Six trials of each threat level were presented in a randomized order. For all levels, approach choices produced the reinforcer while avoidant choices lowered the highlighted level to 1. Instructions stated that failing to respond would produce the prompt "Lose $1", and $1 would be deducted from their total. At completion, ratings of threat and loss expectancy were obtained for each threat level.

Renewal Testing in Context A

At the start, ratings of threat and loss expectancy were obtained for each threat level prior to presentation of the AP-AV task. Next, participants completed the 10 min AP-AV task with Pavlovian threat extinction in effect. Task instructions appeared on a screen with a white background. Instructions were the same as those used for the AP-AV task completed earlier in

Context A and edited to include the statement “YOU ARE NOW BACK IN SECTOR A”. On each trial, a $0.10 reinforcer was made available in the presence of one highlighted threat level displayed on the alien threat meter. Six trials of each threat level were presented in a randomized order. Approach choices produced the $0.10 reinforcer, while avoidant choices lowered the highlighted threat level to 1. Thus, the loss contingency was suspended. Instructions stated that failing to respond would produce the prompt “Lose $1”, and $1 would be deducted from their total. At completion, ratings of threat and loss expectancy were obtained for each threat level.

Dependent Measures

Approach and avoidance responses were made by pressing buttons 1 or 2 on a computer keypad. Choice time was measured from the onset of the main display to a key press. The effects of escalating threat were assessed by examining changes in the probability of avoidance and approach responses and choice times. No trials were excluded from the analysis. Renewal of avoidance was defined as sustained avoidance of escalating threat during testing.

SCR provided a measure of fear/threat reactivity. SCR analysis was performed following published recommendations (Boucsein et al., 2012) with *Ledalab*, a *Matlab* based software package that performed event-related analysis of phasic activity associated with the CS onset. Data were log-transformed and range corrected across conditions to attain statistical normality, reduce error variance (Lykken & Venables, 1971), and facilitate comparisons among conditions. Due to equipment and experimenter recording errors, SCR data were not obtained for three participants and SCR data were not obtained for one participant during the threat learning posttest. Preprocessing of SCR involved two steps. First, for each participant a mean percent maximal SCR deflection was calculated for each threat level. The mean percent maximal SCR represents the mean of the absolute differences between the maximal amplitude deflection 1 s

before the 3 s choice phase and the maximal amplitude deflection during the 3 s choice phase. Second, for each participant, three mean percent maximal SCR deflections were calculated by creating bins for threat levels 1-3, 4-7 and 8-10 (Schlund et al., 2016). The rationale for this approach was to increase statistical power due to the small sample size. Because of between subject variability, individual SCR differences were calculated and plotted by subtracting the mean for bin 1-3 (baseline with *p* of loss = 0) from the mean for bin 4-7 and bin 8-10 (Figure 8). No trials were excluded from the analysis. Renewal of SCR was defined as increasing SCR with escalating threat during testing.

Self-report data consisted of threat level-specific retrospective ratings of feeling threatened and loss expectancy. After each condition, each threat level was individually displayed (randomized order) and ratings were obtained in two categories: Threat ("Please rate how much you felt threatened when the level was at <NOW>?") was measured using a 9-point scale (1 = *None*, 5 = *Moderate*, 9 = *Severe*); loss expectancy ("Please rate how much you would expect (likelihood) to lose money (if you did not choose to avoid) when the level was <NOW>?") was measured using a 9-point scale (1 = *Never*, 5 = *Uncertain*, 9 = *Definite*). Renewal of ratings was defined as increasing ratings with escalating threat during testing.

Statistical Analyses

For each participant, all trials were included in the calculation of descriptive measures. For group analyses, the assumption of sphericity was tested using Mauchly's test and when violated ($p<.05$), a Greenhouse-Geisser correction was used. Within condition changes in avoidance, threat and loss expectancy ratings, and SCR across threat levels were examined using one-way repeated measures analysis of variance. Between condition changes (A-B, B-C) were examined using two-way repeated measures analysis of variance with Context (A,B or B,C),

threat levels (1-10), and bins (1-3, 4-7, 8-10), as appropriate, as within-subject factors. Post-hoc pairwise comparisons used a Bonferroni correction. Within condition changes in SCR for a group of five participants that failed to show avoidance renewal were examined using the Friedman test, which is a non-parametric alternative to repeated measures ANOVA. Paired *t*-tests with a Bonferroni correction were employed to examine between condition differences in percent avoidance and number of earned reinforcers. Criterion α was set to .05.

Results

Figure 3 about here

Renewal of avoidance. Figure 3 presents individual and group results. In Context A (Figure 3, left panel), escalating threat produced a significant increase in avoidance, $F(3, 57) = 227$, $p < .001$, $\eta_p^2 = .923$, which followed a linear trend, $F(1, 19) = 3689$, $p < .001$, $\eta_p^2 = .995$. Visual inspection of Figure 3 shows participants consistently transitioned from approach to avoidance (AP-AV transitions) between levels 5-7. Escalating threat was associated with a significant change in choice times, $F(5.2, 97.9) = 16.27$, $p < .001$, $\eta_p^2 = .461$, which followed a quadratic trend, $F(1, 19) = 45.54$, $p < .001$, $\eta_p^2 = .706$. Thus, escalating threat was associated with an inverted U-shaped distribution of choice times, with the slowest responses occurring midway, near AP-AV transitions.

Following Threat Extinction in Context B (Figure 3, middle panel), the AP-AV task was presented with Pavlovian extinction in effect. Results show a decrease in avoidance, such that all participants chose to approach at each threat level. Comparison of percent avoidance at each threat level between Context B and Context A yielded evidence of a significant context (A, B) x

threat level (1-9) interaction, $F(3, 57.8) = 228$, $p < 0.001$, $\eta_p^2 = .923$, such that avoidance was lower in Context B across threat levels. There was also a significant context x threat level interaction for choice times, $F(9, 171) = 11$, $p < .001$, $\eta_p^2 = .367$, with times significantly faster across levels in Context B than Context A. Lastly, the number of earned reinforcers significantly increased from Context A ($M = 27.45$, $SD = 3.25$) to Context B ($M = 59.8$, $SD = 0.41$), $t(19) = 44.9$, $p < .001$, $d = 10.05$, as approach increased.

Renewal of avoidance was observed during testing in Context A with Pavlovian extinction in effect during the AP-AV task (Figure 3, right panel). Participants exhibiting avoidance renewal showed transitions from approach to avoidance between levels 5-7. A comparison of percent avoidance at each threat level during renewal testing between Context A and Context B showed a significant context (A, B) x threat level (1-9) interaction, $F(3.2, 61.3) = 38.7$, $p < .001$, $\eta_p^2 = .671$, with avoidance increasing more steeply across threat levels in Context A than Context B. There was also a significant context x threat level interaction for choice times, $F(4.4, 83.5) = 3.84$, $p = 0.005$, $\eta_p^2 = .168$, such that times were consistently lower in Context B, particularly during the mid-range levels. Moreover, during renewal testing in Context A, escalating threat produced a significant change in choice times, $F(3.8, 72.7) = 4.04$, $p = 0.006$, $\eta_p^2 = .884$, which followed a quadratic trend, $F(1, 19) = 14.32$, $p = 0.001$, $\eta_p^2 = .948$. Thus, escalating threat was associated with an inverted U-shaped distribution of choice times, with the slowest responses occurring midway, near AP-AV transitions. Finally, increasing avoidance during renewal testing significantly reduced the number of earned reinforcers from Context B ($M = 59.8$, $SD = 0.41$) to renewal Context A ($M = 33.1$, $SD = 14.46$), $t(19) = 8.25$, $p < .001$, $d = 1.84$.

Figure 4, 5 and 6 about here

Detailed analyses of individual subject results appear in Figure 4, which highlights between subject differences during renewal testing in Context A. Individual subject heat maps show the distribution of approach and avoidance choices for each threat level and AP-AV transitions across six blocks of trials. A comparable heat map is provided for the group in Figure 5. The individual subject plots presented in Figure 4 enable a clear assessment of avoidance renewal. Figure 4A shows that fourteen participants exhibited renewal of avoidance characterized by continual choices to avoid during threat levels 4-6 across the six blocks of trials. In contrast, Figure 4B shows six participants with marked decreases in avoidance and increases in approach across blocks. These between subject differences warrant closer examination. For simplicity, we subdivided participants into Avoidance Renewal and No Avoidance Renewal groups and below we describe an analysis designed to identify how SCR differences in Threat Learning may have modulated the emergence of avoidance renewal.

Figure 6 illustrates an additional novel finding observed during renewal testing in Context A. Plots highlight the relationship between percent avoidance and the threat levels at which participants transitioned in Context A from approach to avoidance both at initial testing and during renewal testing. Results show a significantly larger increase in percent avoidance during renewal testing in Context A (M = 57.6, SD = 14.7) than during initial testing in Context A (M = 48.5, SD = 8.7), $t(14) = 2.65$, $p = .009$), $d = .71$. An associated significant decrease in the threat level associated with transitions from approach to avoidance occurred between initial testing (M = 6.3, SD = .91) and renewal testing in Context A (M = 5.3, SD = 1.49), $t(14) = 2.61$, $p = .01$, $d = .71$. Importantly, this pattern was present for most participants. However, the reasons for the observed increase in avoidance are unclear. Further research will be needed to determine

whether the increase is a characteristic of avoidance renewal following Pavlovian extinction or related to the methodology used in this study.

Figures 7 and 8 about here

Renewal of self-reports. Figure 7 presents individual and group self-report ratings. During threat conditioning in Context A (Figure 7, left panel), results reflect successful differential conditioning, such that escalating threat produced increases from pretest to posttest in ratings across levels. Comparison of pretest and posttest ratings across threat levels yielded evidence of a significant context (pre, post) x threat level (1-9) interaction for feeling threatened, $F(4.7, 88.9) = 196$, $p < .001$, $\eta_p^2 = .912$, and loss expectancy, $F(4.0, 76.7) = 80.7$, $p < .001$, $\eta_p^2 = .810$. Specifically, findings indicate higher ratings of both feeling threatened and expectancies of loss at post-test than at pre-test as threat levels increased.

Pavlovian threat extinction in Context B (Figure 7, middle panel) significantly reduced ratings. Comparison of Context B to Context A ratings across levels yielded results that showed a significant context (A, B) x threat level (1-9) interaction for feeling threatened, $F(4.1, 77.3) = 205$, $p < .001$, $\eta_p^2 = .916$, and loss expectancy, $F(3.5, 65.9) = 155$, $p < .001$, $\eta_p^2 = .891$, with lower ratings evident in Context B, particularly at higher threat levels. Additionally, within Context B, escalating threat did not increase ratings of feeling threatened, $F(9, 171) = 1.285$, $p = 0.248$, $\eta_p^2 = 0$, or loss expectancy (all ratings were 1).

Renewal testing in Context A for ratings highlighted a renewal effect (Figure 7, right panel). This was statistically evaluated by comparing ratings across threat levels between renewal testing in Context A before the AP-AV task and Context B. Results showed a significant

context (A, B) x threat level (1-9) interaction for feeling threatened, $F(4.2, 81.1) = 278$, $p < .001$), $\eta_p^2 = .936$, and loss expectancy, $F(2.8, 53.7) = 237$, $p < 0.001$, $\eta_p^2 = .926$. Additionally, within Context A, escalating threat was associated with significant increases in ratings of feeling threatened, $F(4.2, 79.5) = 303$, $p < .001$, $\eta_p^2 = .941$, which followed a linear trend, $F(1, 19) = 1757$, $p < .001$, $\eta_p^2 = .989$. Similar increases were evident for loss expectancy, $F(9, 171) = 237$, $p < .001$), $\eta_p^2 = .926$., which also followed a linear trend, $F(1, 19) = 1775$, $p < .001$, $\eta_p^2 = 989$. Escalating threat was again associated with significant increases in ratings of feeling threatened, $F(1.9, 37.7) = 30.1$, $p < .001$, $\eta_p^2 = .613$, and loss expectancy, $F(1.7, 33.3) = 31.8$, $p < .001$, $\eta_p^2 = .626$, after subjects completed the AP-AV task. Relationships were linear for both feeling threatened, $F(1, 19) = 44.5$, $p < .001$, $\eta_p^2 = .701$, and loss expectancy, $F(1, 19) = 43.8$, $p < .001$, $\eta_p^2 = .697$.

Lastly, a comparison of threat ratings before and after the AP-AV task showed a significant decrease from pre- to post-task. Results showed significant main effects for when ratings were performed (pre- or post-task), $F(1, 19) = 6.85$, $p = .017$, $\eta_p^2 = .265$, and escalating threat, $F(2.5, 47) =$, $p < .001$, $\eta_p^2 = .88$. These main effects were qualified by an interaction, $F(2.3, 43.4) = 5.4$ $p = .006$, $\eta_p^2 = .221$. Similarly, a comparison of loss expectancy ratings before and after the AP-AV task revealed significant main effects for when ratings were performed, $F(1, 19) = 11.69$, $p = .003$, $\eta_p^2 = .381$, and escalating threat, $F(2.4, 45.9) = 141$, $p < .001$, $\eta_p^2 = .876$. The main effects were also qualified by an interaction, $F(2.1, 39.5) = 6.59$, $p = .003$, $\eta_p^2 = .258$. The statistically significant declines in both ratings resulted from substantially lower ratings following the AP-AV task for the five participants that did not exhibit renewal. To illustrate these between-subject differences, Figure 8 shows ratings for the group of participants that showed renewal (Renewal Group) and those that did not (No Renewal Group).

Figures 9 about here

Renewal of SCR. The effects of escalating threat on SCR in each context are shown in Figure 9. Larger SCR values reflect increases in sympathetic nervous system arousal and sweat gland activity. To increase power, threat levels were grouped into three bins (1-3, 4-7 and 8-10), with the resulting mean probabilities of loss: 0.0, 0.29 and 0.83. Individual SCR differences plotted were calculated by subtracting the mean percent maximal deflection for bin 1-3 from the mean percent maximal deflections for bins 4-7 and 8-10. During pretesting in Context A (Figure 9A), escalating threat produced no significant changes in group SCR, $F(2, 32) = 0.723$, $p = 0.446$, $\eta_p^2 = .043$, demonstrating that levels on the vertical bar were initially non-threatening. During Threat Learning in Context A (Figure 9B), escalating threat produced significant changes in group SCR, $F(2, 32) = 4.27$, $p = 0.023$, $\eta_p^2 = .211$, which followed a linear trend, $F(1,16) = 8.709$, $p = 0.009$, $\eta_p^2 = .352$. Post-hoc analyses indicated SCR was largest in bin 8-10, compared to bins 1-3 ($p = .028$) and 4-7 ($p = .999$). The increase in SCR with escalating threat highlights successful differential conditioning, in which SCR was smallest when threat was absent (bin 1-3) and increased across bins as threat escalated.

As shown in Figure 4, a subset of participants failed to show renewal of avoidance. It is plausible that failure in differential conditioning during the Threat Learning condition may account for the absence of avoidance renewal for these individuals. To examine this hypothesis, separate analyses examined SCR data for participants in the Avoidance Renewal (N = 12) and No Avoidance Renewal (N = 5) groups. Three participants were not included because SCR data were not collected. Results in Figure 9C show that escalating threat produced significant changes

in SCR for the Avoidance Renewal group, $F(2, 22) = 6.69$, $p = 0.005$, $\eta_p^2 = .379$, which followed a linear trend, $F(1,11) = 11.410$, $p = 0.006$, $\eta_p^2 = .509$. Post-hoc analyses indicated larger SCR in bin 8-10 compared to bins 1-3 ($p = .018$) as well as larger SCR in bin 4-7 compared to 1-3 ($p = .039$). In contrast, Figure 9D shows that no significant changes in SCR were found for the No Avoidance Renewal group, $\chi^2(2) = 1.2$, $p = 0.549$, $V = .23$. These results suggest that these individuals did not exhibit renewal of SCR during renewal testing in Context A due to a failure of SCR conditioning in the Threat Learning condition.

During Threat Extinction in Context B, no significant changes were found in group SCR, $F(2, 32) = 0.887$, $p = 0.12$, $\eta_p^2 = .007$. Similarly, no significant changes were found in SCR when participants were subdivided into Avoidance Renewal (Figure 9E), $F(2, 22) = 1.574$, $p = 0.23$, $\eta_p^2 = .125$, and No Avoidance Renewal groups (Figure 9F), $\chi^2(2) = 1.2$, $p = 0.549$, $V = .23$. Lastly, during renewal testing in Context A with extinction in effect during the AP-AV task (Figure 9F), no significant SCR changes were observed in the group, $F(2, 32) = 2.50$, $p = 0.098$, $\eta_p^2 = .135$. Similarly, no significant changes were found in SCR when subdivided into Avoidance Renewal (Figure 9G), $F(2, 22) = 0.808$, $p = 0.459$, $\eta_p^2 = .068$, and No Avoidance Renewal groups (Figure 9H), $\chi2(2) = 2.8$, $p = 0.247$, $V = .33$.

Discussion

This purpose of this multimodal, laboratory-based treatment study with healthy adults was to examine fear/threat renewal and avoidance renewal. An ABA context renewal design was used along with an AP-AV task in which a monetary reinforcer was available concurrently with a series of parametrically increasing money loss threats that varied across trials. Approach choices produced a reinforcer or probabilistic loss, while avoidant choices prevented loss and forfeited reinforcement. Renewal testing involved a return to Context A with Pavlovian threat

extinction in effect during an AP-AV task. Results showed renewal, in which escalating threat was associated with increasing avoidance in most participants and increasing ratings of threat and loss expectancies, but no significant changes in SCR. Overall, our main predictions regarding renewal of avoidance and threat and loss expectancies were supported and consistent with prior human basic and clinical studies showing renewal of avoidance and ratings but not renewal of physiological indices of fear (Mystkowski et al., 2002; Neumann et al., 2007). The present findings also replicate and extend results reported by Schlund et al. (2016) which showed escalating threat was associated with increasing ratings of threat and loss expectancy, transitions from approach to avoidance, and increased choice times near AP-AV transitions.

The absence of SCR renewal during AP-AV may appear to contradict results of prior studies using Pavlovian fear conditioning and extinction paradigms. However, our results showed significant differential conditioning of SCR in the group in Context A, as well as differential SCR in participants exhibiting avoidance renewal. Extinction of SCR in Context B was also successful. The failure to observe SCR renewal may stem from any number of factors, including multiple exposures to the AP-AV task which has been associated with SCR declines to high (8-10), but not low (4-7), conditioned threats (Schlund et al., 2016). It is also plausible that SCR insensitivity to escalating threats during renewal testing occurred because avoidance prevented losses. Comparable fear reductions have been reported in human functional neuroimaging studies in which there are significant decreases in prefrontal and limbic activation in regions associated with fear expression during avoidance learning (Boeke, Moscarello, LeDoux, Phelps, & Hartley, 2017), sustained avoidance responding (Schlund, Hudgins, Magee, & Dymond, 2013), and successful compared to unsuccessful avoidance (Schlund, Brewer, Richman, Magee, & Dymond, 2015). These findings also parallel those reported in research on

the controllability of aversive stimuli (Seligman, Maier, & Solomon, 1971). To minimize potential SCR interactions with avoidance responding during renewal testing, it may be necessary for renewal testing of SCR to occur independently of renewal testing for avoidance.

The present findings hold important implications for the treatment of anxiety disorders in typically developing adults and children. First, these findings suggest that conducting Pavlovian fear extinction in only a single context may not be adequate to prevent avoidance renewal for some individuals. Researchers have long emphasized the importance of conducting exposure across multiple contexts to prevent fear renewal (Abramowitz, 2013; Bouton, 2002); indeed, some evidence indicates that outside-of-session exposure frequency is associated with decreases from pre- to post-treatment in clinician ratings of patients' anxiety symptoms (Tiwari et al., 2013). The present findings point to a need to examine whether such varied repetition is essential to prevent avoidance renewal as well.

Second, these findings suggest that it may be important to measure the success of exposure treatment in multiple ways. Our findings showed renewal of avoidance and ratings, but not SCR. Extinction that appears successful when indexed using one measure may appear less effective—or even ineffective in the long term—when others are included. An important next step in this line of work will be to examine whether extinction must be consistent according to multiple measures of both fear and avoidance, in varied contexts, to minimize the risk of renewal. Clarifying which indices best capture enduring and functionally relevant change could assist clinicians in efficiently and effectively evaluating treatment success.

Third, this study's results point to the importance of considering individual variability in patterns of response during exposure treatment. Our data suggest that people differ in their paths to avoidance renewal, with some showing immediate and full renewal and others showing

weaker or more gradual declines. These findings point to a need for clinicians to be prepared to personalize exposure processes for individual clients. Researchers have identified the potential value of varying stimulus intensities across exposures (rather than presenting stimuli in a graded and hierarchical order) for some clients (Kircanski et al., 2012), and our findings suggest that careful attention to other factors that might impede or enhance extinction learning is warranted.

Although the results of the current study have direct implications to the treatment of anxiety disorders in typically developing individuals, the findings are also relevant to understanding cases of failure to maintain treatment effects for negatively reinforced problem behaviors exhibited by individuals with neurodevelopmental disorders. In applied settings where behavior analysts often treat escape/avoidance-maintained problem behaviors, such as aggression, relapse is not uncommon and is often thought to result from poor treatment integrity by parents, guardians, and other caregivers (Kelley, Liddon, Ribeiro & Podlesnik, 2015). However, the present findings illustrate that renewal might also account for relapse of escape/avoidance-maintained behavior following extinction. Conditions supporting renewal may originate with difficulties centered on stimulus control via specific stimuli within different environmental contexts where the treatment is and is not implemented. For example, avoidance/escape behavior that has a rich history of reinforcement in one context (e.g., home), but which is reduced through extinction in another context (e.g., school), may evidence renewal in the home setting, even if caregivers implement the treatment with high procedural integrity (Podlesnik et al., 2017). Moreover, transitioning from a training context to a novel context without a lengthy history of reinforcement can also result in renewal (Bouton, Todd, Vurbric, & Winterbauer, 2011). Therefore, the present findings suggest practitioners should plan and prepare caregivers for possible renewal of negatively reinforced problem behavior in treatment and non-

treatment contexts *even when* the treatment is implemented with high levels of procedural integrity (Kelley et al., 2015).

Notwithstanding the above, the present study has several limitations which warrant further empirical attention. First, future studies should evaluate renewal using variants of Pavlovian and response-prevention extinction procedures aimed at augmenting exposure therapy (Vervliet et al., 2015, 2017). With such procedures, avoidance responding is either possible or prevented, the aversive event is withheld, and is then tested for renewal. Experimental psychopathology research indicates that both fear and avoidance may renew under these conditions (Vervliet et al., 2017). Second, our threat learning phase was 10 min in duration and stability was inferred through visual inspection of loss expectancies. Although only one participant required re-exposure to threat learning, further trials with the threat level indicators as putative CS- and CS+ may have been needed to ensure differential threat (fear) conditioning in all participants. Indeed, adopting a predetermined acquisition criterion would also increase the number of data points/participants available for analysis (Lonsdorf et al., 2017; Ney et al., 2018). Third, the present procedures did not involve electric shock, which is commonly used as US in fear-conditioning and avoidance learning studies. The use of an aversive outcome other than money loss may well serve to enhance conditioned fear/threat responses and subsequent renewal of fear and avoidance. While studies on reinstatement of fear (Haaker, Golkar, Hermans, & Lonsdorf, 2014) and avoidance (Cameron, Schlund, & Dymond, 2015) have used shock, clearly further work is needed on renewal with different types of aversive events (e.g., shock, loud noise, unpleasant images, etc.). Finally, the present findings were obtained with an ABA renewal design; it is important therefore to replicate and extend the current findings with other renewal designs such as ABC (Urcelay et al., 2019).

There are several promising future directions for research on renewal of human avoidance that have implications for translational research on anxiety. One area concerns the neural mechanisms of fear renewal which have largely been identified using nonhumans. Results of nonhuman anatomical and electrophysiological studies indicate central roles for the hippocampus, prelimbic cortex and amygdala as well as the connections between them in fear renewal (Chen, Wang, Wang & Li, 2017). Consistent with nonhuman studies, human fMRI research shows the involvement of the amygdalar-hippocampal complex, insula and ventromedial prefrontal cortex in fear renewal (Hermann, Stark, Milad & Merz, 2016). To date, no human neuroimaging investigations have tackled avoidance renewal, but the present study does offer a proven methodology for addressing questions about neural mechanisms of avoidance renewal. Other issues worthy of further research concern individual and sex difference variables known to modulate fear and avoidance including the effects of gonadal hormones on brain regions implicated in fear extinction (Lebron-Milad & Milad, 2012) and avoidance (Aupperle, Sullivan, Melrose, Paulus & Stein, 2011; Sheynin, et al., 2014) as well as the role of stress in subsequent avoidance renewal (Drexler, Merz, & Wolf, 2018).

In conclusion, this laboratory-based treatment study found renewal of avoidance and self-reports of feeling threatened and loss expectancies, but not SCR, when participants were tested in a return to the original training context. Echoing the recommendations of Craske et al. (2018), our findings speak to the importance of measuring avoidance behavior in its own right (not merely as a proxy of fear) and of tracking simultaneous increases in approach behavior in future research aimed at augmenting exposure therapy for anxiety disorders.

Conflict of interest

All authors have no conflict of interest.

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Figure Captions

Figure 1. *Threat learning screen display.* During threat learning, increasing 'levels' on a vertical bar were paired with increasing probabilities of $1 money loss. Each trial presented a "NOW" cue on the vertical bar followed 3 s later by the probabilistic loss.

Figure 2. *Approach-avoidance (AP-AV) task screen displays.* Choice and outcome displays presented during the AP-AV task. On each trial, a reward and a (conditioned) threat level were presented together. Participants were given a choice between approach (Press #1), which produced $0.10 *or* the probabilistic $1 loss, and avoidance (Press #2), which prevented loss and forfeited reinforcement. Each trial consisted of a 3 s choice period, a 750 ms outcome period and variable 5-7 s intertrial interval. Instructions and different screen colors informed participants of the current context (either A or B).

Figure 3. *Individual and group approach-avoidance results.* Each function plotted represents a participant and group means are highlighted by a thick grey line. Open bars in the plot displaying number of reinforcers obtained highlight six participants that did not exhibit avoidance renewal.

Figure 4. *Renewal testing in Context A: individual approach-avoidance performances*. Individual subject heat maps provide a graphical representation of the distribution of approach and avoidance responses for each of ten threat levels over six blocks of trials. [A] Avoidance continued across blocks for fourteen participants (Avoidance Renewal Group). [B] Avoidance declined across blocks for six participants (No Avoidance Renewal Group).

Figure 5. *Renewal testing in Context A: group approach-avoidance performance*. The heat map provides a graphical representation of changes in the group mean percent avoidance for each of ten threat levels over six blocks of trials.

Figure 6. *Increase in avoidance during renewal testing.* Participants that showed avoidance renewal (N=14) exhibited an increase in the frequency of choosing to avoid (left plot) and transitioned from approach to avoidance at lower threat levels (right plot) during renewal testing in Context A compared to initial testing in Context A.

Figure 7. *Individual and group self-reports*. Each function plotted represents a participant and group means are highlighted by a thick grey line.

Figure 8. *Self-reports during renewal testing in Context A following the AP-AV task.* The left column shows ratings for participants that exhibited avoidance renewal (Avoidance Renewal Group). The right column shows ratings for participants that did not exhibit avoidance renewal (No Avoidance Renewal Group).

Figure 9. *Individual and group SCR changes.* Each function plotted represents a participant and group means are highlighted by a thick grey line. Binned threat levels (1-3, 4-7, 8-10) and associated mean loss probabilities appear on the x-axis. (See Methods for how individual SCR differences were calculated). [Context A] Threat Learning: No significant changes in group SCR were found at pretest. During Threat Learning, there were significant changes in group SCR, highlighting successful differential conditioning. Subdividing participants into two groups that did or did not exhibit avoidance renewal revealed significant SCR changes only in group that exhibited avoidance renewal. [Context B] Threat Extinction: Both group's SCR showed no significant changes. [Context A] Renewal Testing during the AP-AV task: Both group's SCR showed no significant changes. (Bars = Significant post-hoc differences. *Outlier: SCR response of .80 in bin 8-10.)